VIRAL HEMORRHAGIC FEVERS

FLAVIVIRUSES

Flaviviruses are a particular group of viruses responsible for causing some of the worst human diseases, such as yellow fever, dengue hemorrhagic fever, Japanese encephalitis and tick-borne encephalitis. These viruses, which have been known to plague mankind for centuries, afflict people of all ages and races and cause thousands of deaths every year. Although many countries have been successful in controlling these menaces, they continue to cause large epidemics in many areas of Asia, Africa and Latin America.

Despite strides in medical technology and public sanitation, flaviviruses are still capable of causing regular outbreaks because effective vaccines against these agents have not been developed. Researchers have been trying to understand flaviviruses in greater detail in the hope of discovering something about their pathology that could lead to the creation of highly protective and long-lasting vaccines. Because flaviviruses are important human pathogens, it is important that people understand more about the nature of these viruses, the diseases they cause, the way they are transmitted and how they can be controlled.

The yellow fever virus, the first flavivirus shown to cause a human disease, frequently is used as a model to describe the flavivirus genus, whose members share similar molecular and pathological properties; for instance, protein and genetic composition, replication mechanism and infection pathway. Because the yellow fever virus was the first flavivirus to be discovered and clinically described, its genus was titled after its Latin name – "flavi," the Latin word for "yellow" – hence, "flavi-virus."

The yellow fever virus was once greatly feared and is still capable of causing large epidemics. The virus originated in Africa and was brought to the Americas with European colonization and the introduction of slaves during the 17th and 18th centuries. For many decades following its introduction to the Americas, yellow fever was continuously epidemic among Native Americans and European settlers in the Caribbean zone. It did not take long for the virus to spread to the southern and eastern coasts of the United States, where it struck major cities and ports such as Philadelphia, New York and Boston. The virus also spread up the Mississippi River from New Orleans, causing large outbreaks in cities along the river. The disease afflicted most urban dwellers and caused death rates of 20 percent or more of a city's original population, resulting in panic that led people to flee from their towns. The virus also was transported overseas to Europe, where it caused thousands of deaths in Italy, France, Spain and England in the 18th century.

Today, yellow fever still can appear in epidemic form in the tropical and subtropical regions of Africa, Asia, Latin and Central America, Indonesia and northern Australia. In Africa and Latin America, reported outbreaks can reach up to hundreds of thousands of cases in a year, as in Nigeria between 1986 and 1991. Annually, between 5,000 and 6,000 cases in Africa and 300 to 500 cases in Latin America are reported officially, but these figures are significantly underestimated. In recent years, epidemics of yellow fever also have spread to countries where

the disease has rarely appeared, such as Peru, Bolivia and Cameroon. In 1990, an outbreak in Cameroon caused as many as 20,000 cases, with 1,000 deaths.

The yellow fever virus is transmitted in two consecutive cycles involving monkey and human hosts and mosquitoes. In the first cycle, the virus is transmitted by the mosquito Aedes africanus and other Aedes mosquitoes (in Africa) or by Haemogogus mosquitoes (in the Americas); monkeys serve as its reservoir; and the primary humans infected are those who enter deep forests and jungles. In the second cycle, the domestic mosquito Aedes aegypti, which lives in close relationship with humans, may transmit the virus, with humans being the sole hosts in the cycle. An epidemic is established when an individual infected in the first cycle passes the virus to Aedes aegypti, which spreads the infectious agent to any urban dweller in the second cycle.

Yellow fever is characterized mainly by hemorrhage (excessive bleeding), caused by the growth of the virus in the kidney and heart, and jaundice (yellowish discoloration of tissues and bodily fluids), caused by the growth of the virus in the liver. The disease begins abruptly with fever, chills, anorexia, nausea, vomiting and minor bleeding. After three days, the initial symptoms reach their worst state, and additional symptoms such as jaundice, dehydration and severe hemorrhages begin to appear. Death, which occurs in about 20 percent to 50 percent of all cases, usually happens between the seventh and 10th day of illness as a result of extensive liver damage. This final stage is generally preceded by deepened jaundice, uncontrolled hemorrhages, rising pulse, agitated delirium and coma – the terminal signs.

Other flaviviruses have many properties in common with the yellow fever virus. Most of them are transmitted in cycles involving animals that serve as reservoirs (such as monkeys, bats, birds and domestic animals), arthropods that serve as carriers (such as mosquitoes of the genera Aedes, Culex or Haemogogus) and humans that serve as the final host. In addition, most of these viruses affect human populations in the tropical and subtropical areas of the world such as South and Southeast Asia, the Pacific Islands, Africa, the Caribbean and Latin America. The warm climate and heavy rainfall in these areas give rise to ideal breeding grounds for mosquitoes, which like to grow neat irrigated farms, flooded areas, jungles, rain forests and swamps. However, not all flaviviruses follow these rules. The tick-borne encephalitis virus, for instance, is a flavivirus transmitted by ticks of the genus Ixodes, which thrive in temperate regions of Russia and Europe. The virus can affect only humans in areas where its carriers exist; hence, these diseases are usually native to a particular locality. Based on their carriers, flaviviruses can be divided into three major groups: the mosquito-borne group, (which includes the majority of flaviviruses), the tick-borne encephalitis group, and the group that lacks an arthropod carrier (this group is of least medical importance).

A number of encephalitic diseases were recognized in the 19th and 20th centuries and were clinically proven to be caused by flaviviruses. Among these were Japanese encephalitis, St. Louis encephalitis and tick-borne encephalitis. Like yellow fever, these diseases frequently appear in epidemic form and cause thousands of deaths each year.

The encephalitic diseases share many clinical features, as they are all caused by inflammation of the brain. In the typical case, the onset produces symptoms such as severe headaches, fever, chills, nausea, vomiting, anorexia, muscle pain and diarrhea. In the second stage, these symptoms are followed by muscular rigidity, photophobia, hyperexcitability, abnormal tremors and movements, incoordination, paralysis, sensory loss, convulsions and respiratory dysfunction. The death rate, however, varies slightly for each disease. For Japanese encephalitis, death usually

occurs in the fifth to ninth day in fatal cases, and in countries where these diseases are poorly controlled, fatality rates generally range from 20 percent to 50 percent in all age and sex groups, although higher fatality rates are sometimes observed. For St. Louis encephalitis, about 50 percent of patients who have fatal infections die within one week of onset, and 80 percent die within two weeks of onset, with the case fatality rate increasing from 2 percent in young adults to more than 22 percent in the elderly. For tick-borne encephalitis, death occurs within the first week in fatal cases.

Japanese encephalitis is widely distributed in Asia, including Japan, China, India, Indonesia and the Philippines. Every year, around 35,000 cases with 10,000 deaths are reported, but these figures are significantly underestimated. Fewer than 20 cases now occur annually in Japan, but more than 10,000 cases occur in China and India. In tropical areas, there is an endemic pattern of infection, with cases occurring sporadically throughout the year. In temperate zones, outbreaks have a marked seasonal incidence that corresponds to the density of the mosquito vector and the rate of virus transmission, which both depend on the temperature and the amount of rainfall. The main carriers of the Japanese encephalitis virus are the Culex mosquitoes, such as Culex vishnui (India), Culex gelidus and Culex fuscocephalus (Malaysia, Thailand), Culex annulus (Taiwan) and Culex annulirostris (Guam). The year-round transmission cycle of these viruses involve these mosquitoes, as well as birds and pigs that serve as intermediate hosts.

St. Louis encephalitis is a North American disease that frequently occurs in epidemic form in the United States. The virus predominantly attracts the Ohio-Mississippi Valley, eastern Texas, Florida and California, where its principal carriers, the Culen mosquitoes, are found. In the Ohio-Mississippi basin and in eastern Texas, the distribution of cases is urban-suburban, corresponding to high densities of Culen pipiens and Culex quinquefasciatus, which breed in polluted waters. In Florida, the tropical mosquito Culex nigripalpus is the epidemic vector, whereas in the western states, the principal carrier is Culen tarsalis. Since 1955, nearly 5,000 cases of St. Louis encephalitis have been officially reported in the United States. The disease occurs in epidemic form at approximately 10-year intervals, with small numbers of notified cases (fewer than 50 per year).

Tick-borne encephalitis occurs in an endemic pattern aver a wide area in Europe and eastern Russia corresponding to the distribution of lxodes, Dermacentor, and Haemaphysalis ticks. The intensity of transmission varies from year to year, with increases in small-mammal populations (the principal hosts for immature ticks) followed by rises in tick populations and a higher rate of human infection. The virus is maintained in nature in a cycle involving amplifying hosts such as shrews, moles and hedgehogs, which have relatively stable populations, and large mammals such as goats, sheep, and cattle, which serve as hosts for adult ticks. The disease is contracted by drinking raw milk from these infected domestic mammals, as the virus is excreted into the milk of animals during infection.

Flaviviruses cause many other encephalitic diseases, among them Murray Valley encephalitis, West Nile fever, louping-ill, Rocio, and Powassan. These illnesses also are capable of causing epidemics and produce clinical features similar to those of the other encephalitic diseases. They are also transmitted by mosquitoes or ticks.

The dengue virus has undergone a dramatic expansion in range and has turned into a worldwide disease, causing hundreds of millions of cases of dengue fever each year. The cause of its worldwide spread can be attributed to expanding urban populations and a coincident increase in

the density of its carrier, as well as the introduction of air travel and the rapid movement of infected persons. Dengue fever occurs principally in the tropical areas of Asia, Oceania, Africa, Australia and the Americas, with the mosquitoes Aedes aegypti, Aedes polynesiensis, and Aedes scutellaris affecting Asia and the Pacific, and many other Aedes mosquitoes affecting West Africa. Like the yellow fever virus, the dengue virus is transmitted in cycles involving monkey and human hosts and Aedes mosquitoes. The clinical features are similar to those of yellow fever. The initial symptoms include high fever, headaches and muscular pain, which are then followed by increased muscular and bone pain, anorexia, nausea, vomiting, skin rashes and weakness. Although the disease usually is nonfatal, the virus can cause more severe illnesses characterized by hemorrhage – as with dengue hemorrhagic fever – or shock, as with dengue shock syndrome.

Dengue hemorrhagic fever initially produces symptoms similar to those of classic dengue fever but progresses after two to five days to a severe form characterized by restlessness, irritability, rapid respiration, rapid pulse and hypotension. Spontaneous hemorrhages occur, along with many other physiological abnormalities. Without early recognition and appropriate treatment, as many as 50 percent of patients with the severe disease may die. Dengue hemorrhagic fever is a leading cause of death in tropical Asia, where it is endemically established. In Thailand in 1977, for example, the disease was the second leading cause of death due to infectious disease. During the past 30 years, more than 700,000 cases and 20,000 deaths have been reported officially, with major epidemics in China, Vietnam, Indonesia, Thailand and Cuba.

Biological transmission of flaviviruses by arthropods (e.g., mosquitoes, ticks) depends upon the following: ingestion of a blood meal containing the virus, infection of skin cells, escape of the virus into the salivary glands, and secretion of the virus in saliva when refeeding on an animal host. Most flaviviruses, which generally do not have any pathogenic effects on their carriers, are very specific about the kinds of hosts they infect. The differences in their infectiousness depend upon the particular flavivirus involved and the host cell type. Infection is commonly lethal to animal cells, although some do not show these effects and become chronically infected. Mosquitoes and ticks usually remain infected for life and produce extremely high levels of infectious virus particles in the salivary glands.

Many vaccines developed in the past have limitations, including the need for repeated vaccination (the effect wears off after a period of time) and low protective efficacy (vaccinated individuals are vulnerable to the disease). Virologists have conducted research in the following areas in the hope of finding better vaccines: (1) the control of viral RNA synthesis during the course of infection, (2) the assembly of virus particles and (3) the nature of the protein receptors used by flaviviruses to enter cells. These experiments have led to a new way to make effective vaccines out of recombinant flaviviruses constructed from the genetic material of two different virus strains. Such a recombinant shows the characteristics of both parents since it contains portions of their genetic material.

A recombinant can be made from any two flaviviruses; for instance, the yellow fever virus and the dengue virus. The RNA of the yellow fever virus is used as a backbone to hold genes, or specific genetic sequences that code for specific proteins, that are to be sliced out of the RNA of the dengue virus. With the help of techniques in molecular biology, selected genes of the dengue virus are removed and subsequently inserted into specifically chosen regions within the genetic backbone of the yellow fever virus, so that the resulting RNA strand – the genetic material of the new recombinant virus – contains genes from both viruses. However, not all recombinant viruses

created in the laboratory will be living or functional like their parental strains because the survival of a flavivirus depends upon many factors; most importantly, whether or not the genes needed for survival are present in its RNA, and whether or not they are combined in the correct order. In fact, most efforts to construct living virus recombinants in the laboratory are unsuccessful, as it is difficult to arrive at the correct gene combination that can give birth to a living virus. Despite the obstacles encountered through the process, the successful creation of living recombinant viruses has potential implications for the development of an effective vaccine. These living recombinants can be made to be attenuated (weakened and nonlethal) so that they pose no harm to their hosts, yet still possess the antigenic properties of their parents.

Live, attenuated viruses can be used in vaccines to help humans establish protective immunity against real infections by the parental viruses. Vaccines created from these viruses generally induce longer-lasting immunity than do some other vaccines. These viruses replicate and lead to the production of large amounts of antigen over a period of days or weeks that continue to stimulate the immune system. Furthermore, the viral antigens are presented in the context of normal viral infection, and these vaccines induce the 111 range of immune responses from the animal host. The principal difficulty with live virus vaccines is the necessity to attenuate the virus sufficiently so that it does not cause disease, while retaining its potency for vaccination. Despite this difficulty, live attenuated virus vaccines have been extremely successful in the control of viral diseases.

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